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Concepts of Bioequivalence and Therapeutic Interchange

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Abstract The FDA, regulatory agencies, industry, and academia have all made significant progress in determining bioequivalence (interchangebility between generic and the innovator product). The FDA in the United States approves and awards generic medication marketing authorization by applying the regulatory procedures set forth in the Code of Federal Regulations (CFR). The purpose of this article is to review scientific criteria for marketing authorization of generic products.

Keywords Marketing authorization, Generic product, Bioequivalence, Therapeutic interchange

Introduction

The concept of BE has been accepted worldwide by the pharmaceutical industry and national regulatory authorities for over 45 years and it is applied to new as well as generic products. As a result, thousands of high quality generic drugs at reduced costs have become available all over the world. It is vital for the regulatory authorities of each country to guarantee the efficacy and safety of these generic products. The modernization of the New Drugs Regulatory Program made by FDA in 2017 has a mission in protecting and promoting health by making sure that human drugs are safe and effective for their intended use, that they meet established quality standards, and that they are available to patients. Carefully planned and designed bioequivalence studies are the only way to ensure uniformity in standards of quality, efficacy and safety of pharmaceutical products.

Many advancement have been made by the FDA, regulatory authorities, industry and academia to assess bioequivalence (interchangebility between generic and the innovator product). In the United States, the FDA approves and grants marketing authorization of generic drugs by applying the regulatory requirements provided in the Code of Federal Regulations (CFR).

The purpose of this article is to review scientific criteria for marketing authorization of generic products.

Bioequivalence studies are very important for the drug development phase for both new drugs and generic equivalents in the pharmaceutical industry. Their description and the results of generic products are a significant part of the registration dossier submitted by regulatory authorities. The importance of bioequivalence studies is increasing also due to the large growth of the production and consumption of generic products.

Generic products represent approximately 50 % of the whole consumption in many European countries and USA. The search output of bioequivalence study is together with the pharmaceutical quality data of medical product one of the main part of the registration file submitted to a national regulatory authorities. The registration of generic products does not demand complicated and expensive clinical study contrary to original product. The comparison of the original and the generic product via bioequivalence study is suggested as sufficient.

For the approval of generic drug products, bioavailability (BA)/bioequivalence (BE) studies are often conducted to demonstrate that the drug absorption profiles in terms of the extent and rate of absorption of test products are bioequivalent to those of the innovative drug product. BA and BE information has been determined to have practical and public health value for pharmaceutical sponsors, for regulatory agencies, and for patients and practitioners.

Before the pharmaceutical product reaches the patient, it should pass different stages as research, development, clinical research, production, analysis, distribution, marketing and purchasing. Bringing a new product to market is complex and controversial. Lifecycle of innovator product includes development of an active ingredient, formulation development, manufacturing, pre-clinical research on microorganisms and animals, clinical trials on humans and regulatory approval. Thus, the innovator product project is coped with high attrition rates, long timelines, local challenges, industrial risks and large capital expenditures [1].

Pharmaceutical products intended exclusively for export should be subjected by the regulatory authority of the exporting country to the same controls and marketing authorization requirements with regard to quality, safety and efficacy as those intended for the domestic market in that country. Nominally equivalent interchangeable (generic) pharmaceutical products should contain the same amount of the same therapeutically active ingredients in the same dosage form and should meet required pharmacopoeial standards. Regulatory authorities should therefore require the documentation of a generic pharmaceutical product to meet three sets of criteria relating to:

- manufacture (GMP) and quality control;
- product characteristics and labelling; and
- therapeutic equivalence.

Pharmaceutical equivalents have the same amount of the same active pharmaceutical ingredient (salt, ester), same dosage forms and same route of administration. Pharmaceutical equivalence is enough for aqueous solutions, powders for reconstitution as solution and gases. Pharmaceutical equivalence by itself does not necessarily imply therapeutic equivalence. Therapeutic equivalents are pharmaceutical equivalents with same safety and efficacy profiles after administration of same dose. Possible differences (e.g., drug particle size, excipients, manufacturing process or equipment, site of manufacture) could lead to differences in product performance *in vivo*. Marketing authorization of multisource (generic) products needs extensive clinical trials to demonstrate safety and efficacy. Demonstration of equivalence to reference (comparator) product means interchangebility and therapeutic equivalence.

Apart of comparing multisource pharmaceutical product with a reference (innovator), BE studies are employed in pre – and post-approval changes (bridging studies), and additional strengths of existing product. In descending order of preference, the US FDA recommends comparative pharmacokinetic studies, comparative pharmacodynamics studies, comparative clinical trials and comparative *in vitro* tests to evaluate bioavailability and determine bioequivalence for both innovative drug products and generic drug products [2].

For the Food and Drug Administration, the definition of bioavailability focuses on the processes by which the active ingredients or moieties are released from an oral dosage form and move to the site of action [3]. Bioavailability is the rate and extent to which a substance or its active moiety is delivered from a pharmaceutical form and becomes available in the general circulation. Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

The bioequivalence studies, pharmacodynamic studies and clinical trials should be carried out in accordance with good clinical practice (GCP) for trials on pharmaceutical products, with good manufacturing practice (GMP) and with good laboratory practice (GLP). A trial of a pharmaceutical product in humans should be scientifically and ethically justified. All research should be conducted in accordance with the ethical principles contained in the current version of the Declaration of Helsinki. All individuals involved in the conduct of any clinical trial must be fully informed of and comply with these principles. Information on the safety and efficacy of the investigational product is required conducting a clinical trial. Investigators involved in a clinical trial are responsible for ensuring

that an investigation is conducted according to the signed statement, the investigational plan and regulations for protecting the rights, safety and walfare of subjects and for the control of drugs.

Comparative pharmacodynamic studies

Comparative pharmacodynamic studies in healthy volunteers or patients may be conducted for establishing equivalence between two pharmaceutical products. This may be necessary if the drug in biological liquids cannot be determined quantitatively with sufficient accuracy and sensitivity. Furthermore, pharmacodynamic studies in humans are required if measurements of drug concentrations cannot be used as surrogate end-points for the demonstration of the efficacy and safety of the particular pharmaceutical product (eg., topical and inhalation administration, oral dosage forms that are not absorbed into systemic circulation) [4]. The acceptance criteria of equivalence in this study should be established by considering pharmacological activity of each drug. Generally, high between-subject and/or within-subject variabilities are expected using PD parameters endpoints. This raises ethical issues regarding the larger number of subjects exposed to the drug as well as financial concerns [5].

Comparative clinical studies

A clinical endpoint BE study is a comparative clinical study in humans that is applicable for drugs delivered directly to sites of action and drug products that have negligible systemic uptake. When there is no identified pharmacokinetic or pharmacodynamic measure, a comparative clinical trial must then be performed in order to demonstrate bioequivalence between two formulations. While in PK study is used single dose in healthy subjects, in clinical trial are used multiple doses in patients. The same statistical principles are applied as in bioequivalence studies. Apart of providing a direct assessment in patients that is reassuring to clinicians, clinical trials are associated with a number of challenges as well. Clinical endpoints are associated with high variability and low sensitivity that make such studies less reliable and less efficient. In clinical trials, product-specific guidance may not be available and some products require multiple studies. There is a difficulty to achieve consistency between studies (study design, study population, BE endpoints). Time of measurement may not be sensitive to detect the difference between products. Also, in these studies, rating scale is subjective and variable and the number of patients enrolled is usually much higher than that required in bioequivalence studies. Compared with PK and PD studies, clinical trials are risky, complicated, insensitive, time-consuming and very expensive.

Comparative *In vitro* studies

In vitro dissolution testing is an important tool in drug development and quality evaluation of the pharmaceutical dosage forms. During drug development, dissolution testing identifies formulations factors affecting bioavailability of the drug. For local delivery drug products, FDA indicates that bioequivalence may be assessed, with suitable justification, by in vitro bioequivalence studies alone [6]. In vitro methods are less variable and more likely to detect differences between products. The bioequivalence study for BSC (Biopharmaceutical Classification System) class 1 may be waived based on similarity of dissolution profiles, using three different buffers. For the approval of generic drugs, comparative in vitro study becomes a potential surrogate for in vivo bioequivalence and used for achieving biowaivers. Because of poor hydrodynamics and unclear role, it is recommended that its application for this purpose should be kept to a minimum [7]. *In vitro* dissolution testing as the sole documentation of equivalence is not applicable to all dosage forms, but should be reserved for rapidly dissolving drug products [4]. Where a drug substance and drug product do not dissolve with sufficient rapidity, *in vitro* dissolution methods may still be used to document equivalence using appropriately validated dissolution methodology including an *in vitro/in vivo* correlation.

Comparative pharmacokinetic studies

Comparative pharmacokinetic study is a gold standard and generally the preferred method for the improvement of the most generic drugs.

There are different types of study design of BE. The more sophisticated design is, the more information can be extracted. Basic designs for BE studies may be parallel, cross-over, replicate and two-stage. Parallel design is optimal for drugs with long half life and suitable for studies in patients with instable diseases. Parallel design sometimes is faster but it has lower statistical power than crossover. A partial replicate design with repeating the reference product and scaling the bioequivalence for the reference variability are proposed for drugs with high within-subject variability. In case of high variability, more regulatory authorities may accept a two-stage or group-sequential bioequivalence design using appropriately adjusted statistical analysis [8].

A two-period, fully balanced, two-sequences, single dose, cross-over study design in which each subject is administered the test and reference formulation is still the design of first choice by Regulatory Authorities [3,6,9,10]. It is a globally applied standard protocol for bioequivalence, drug-drug interaction and food effect studies. The disadvantage of a two-way cross-over design is the large sample size of subjects for BE studies with highly variable drugs.

Generally, single-dose PK studies are sufficient for regulatory acceptance. They are recommended for both immediate- and modified-released products as they are more sensitive in assessing the active ingredient released from drug into circulation. Multiple dose studies are required in the case of dose- or time-dependent pharmacokinetics.

The PK study is conducted in a small number of healthy adult volunteers (typically 18 to 24 individuals) [3,6]. The subjects should not take any medication one week before start of study. The drug is administered to the subjects in fasting state. The subjects are randomly selected for each group in the study and the sequence of drug administration is randomly assigned to the individuals. In a typical situation of comparing a test formulation (T) with a reference formulation (R), the two-period, two-sequence cross-over design is the RT/TR design as shown is figure 1.

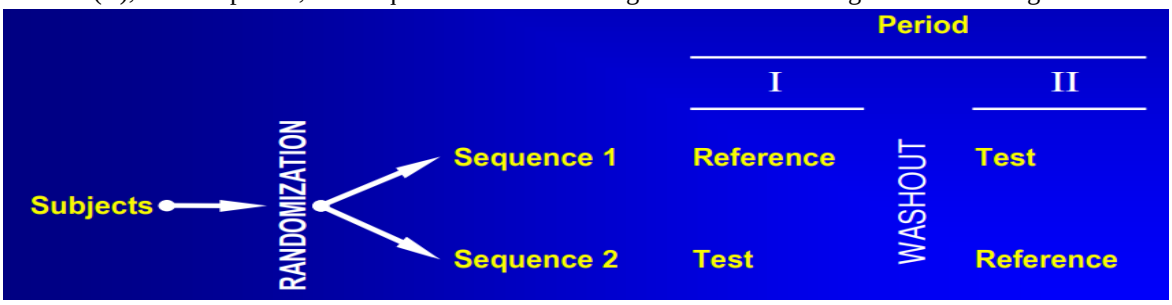

Figure 1: Cross-over design

The administration of each product is followed by an adequate wash-out period of time (more than 5 half-lives) to ensure complete elimination of drug before next administration. Under most of the conditions blood or plasma is collected rather than urine or tissue. Blood samples are drawn at appropriate times to assess absorption, distribution and elimination phases of the drug. For most of the drugs 12-18 samples are recommended including pre-dose sample from each subject. The measurement of drug concentration in collected samples is performed through bioanalytical method. Prior to sample analysis, the selected or developed analytical method is validated in accordance with guidelines [11]. The PK parameters characterizing the rate and extend of drug absorption are then determined. Area under the plasma concentration-time curve (referred to as AUC_{0-t}) is the measure of the extent of bioavailability and is calculated by trapezoidal rule, where t is the last measurable time point. Area under the plasma concentration-time curve from time zero to time infinity ($AUC_{0-\infty}$)

$AUC_{0-\infty} = AUC_t + C_t/\lambda_z$

where C_t is the last measurable drug concentration and λ_z is the terminal elimination rate constant calculated according to an appropriate method. The terminal or elimination half life of the drug should be documented. The PK parameter used to characterize the rate of absorption and the extent of bioavailability is the maximum or the peak drug concentration (Cmax). The maximum time when drug reaches peak concentration (Tmax) is the measure of the rate of absorption. C_{max} and T_{max} are obtained directly from the data without interpolation. Pharmacokinetic parameters like $AUC_{0-\infty}$, AUC_t , λ_z are derived from original data by mathematical calculations or by using software. According to ICH GCP guidelines (followed by USA, Europe and Canada), two medicinal products are

bioequivalent if the 90% confidence intervals (90% CI) of the transformed natural log ratios, between the two preparations of C_{max} , AUC_t and $AUC_{0-\infty}$ lie in the range of 0.8-1.25. Figure 2 illustrates graphically bioequivalence of two preparations after oral administration of drugs (glucophage as reference and metformine as test) to twenty albanian healthy volunteers. [12]

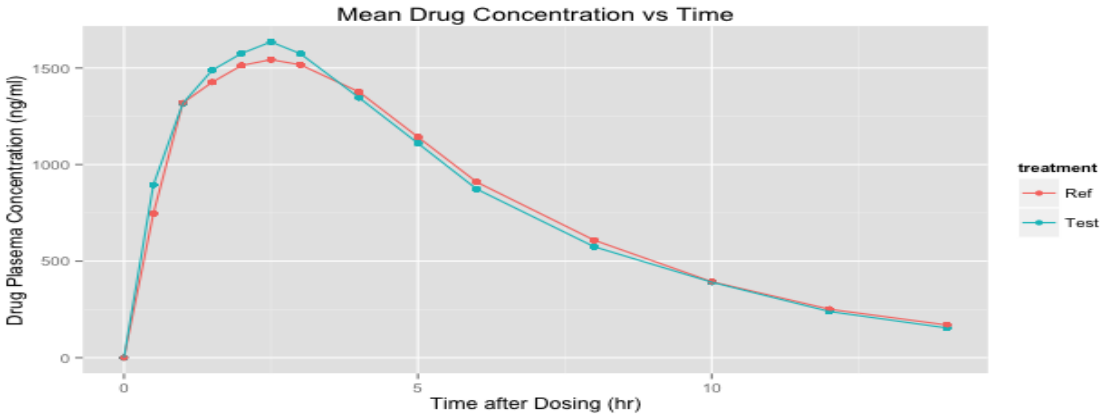

Figure 2: Mean plasma concentration-time curve of metformin, after oral administration of 850 mg to twenty albanian healthy volunteers.

It is already known that it is not enough to bring more generics to the market. Patients should also have confidence in the safety and quality of generic drugs. The FDA review and evaluation process for generic drug applications ensures that these drugs have the same active ingredients and the same conditions of use as their commercial drug. Once a consignment has been approved, the FDA continues to monitor its safety, efficacy, and quality, including through periodic inspections of manufacturing departments, careful evaluation of post-approval changes proposed by manufacturers, and evaluation of any side effects report. To have a stable and competitive market to increase access and to have lower drug prices, in the coming months, the FDA will publish additional guidance and take other important policy steps to assist applicants for additional generic drugs.

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